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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/940,422	08/29/2001	Lorraine Mary Edmeades	1430-272	5500

23117 7590 02/26/2004

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EXAMINER	
SODERQUIST, ARLEN	

ART UNIT	PAPER NUMBER
1743	

DATE MAILED: 02/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/940,422	EDMEADES ET AL.	
	Examiner	Art Unit	
	Arlen Soderquist	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/265,670.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ ~~Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)~~ Paper No(s)/Mail Date *12-18-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The claims are directed to a specific compound and its use for a specific purpose.

2. Claim 13 provides for the use of a compound as a reference marker in testing the stability of a sample of lamotrigine, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

3. Claim 13 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

5. Claim 12-13 are rejected under 35 U.S.C. 102(b,e) as being anticipated by Floyd (WO 97/00681 and US 5,492,510). In the published application and US Patent Floyd teaches a pharmaceutical composition containing lamotrigine. Tables 2 and 3 give results from assays of

the compositions for stability. In Table 2, the first column under the related substances is for the compound 3-amino-5-keto-6-(2,3-dichlorophenyl)-1,2,4-triazine (footnote g), which is the instantly claimed 3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine-5(4H)-one. Footnote a of Table 3 teaches that the assay was a High Performance Liquid Chromatography (HPLC) procedure according to the Analytical Standard. In Table 3, the second column shows the concentration of the instantly claimed compound (see footnote b). On pages 8-10 of the publication and columns 5-6 of the patent a process of producing a pharmaceutical dosage and its stability testing it is outlined. The process includes mixing the components together and drying them into a solid form (steps 1-9), stressing the dried product (step 10), reconstituting the dried product and assaying the product as outlined in tables 3-4 (steps 11-12).

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Floyd as applied to claims 12-13 above, and further in view of Papadoyannis. Floyd does not teach the use of standard solutions.

In the paper Papadoyannis presents an efficient off-line solid-phase extraction (SPE) of lamotrigine (LTG) from human serum and urine prior to HPLC analysis. High extraction recoveries were achieved from C8 bond Elut cartridges (200mg/3ml), using acidic acetonitrile for the elution of LTG and the internal standard, 3,5-diamino-6-(2-methoxyphenyl)-1,2,4-triazine. Isocratic reversed-phase HPLC (RP-HPLC) analysis on octyl silica, using a Lichrosorb

RP-8, 5 μm, 250 × 4.6 mm column and a mobile phase consisting of pH 5.6 0.05M acetate buffer-MeCN (72:28) was sensitive and rapid. The identification of LTG was performed by UV detection at 306nm. The method detected approx. 0.9 ng LTG on-column, using a 20-μL loop, and linearity holds from ~ 0.044 to 7.8 μg/mL in standard solutions. These standard solutions were used to form a calibration chart for determining concentrations and also for checking the day-to-day precision and accuracy. In plasma and urine, the limits of detection are 1.1 and 1.2 ng, respectively, while linearity holds from ~ 0.087 to 3.49 μg/mL. The proposed method was also used for the direct analysis of antiepileptic tablets.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use standard solutions in the Floyd method because as shown by Papadoyannis the standard solutions allow formation of calibration charts for determining concentrations and checking the day-to-day precision and accuracy.

8. Claims 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dreassi in view of Floyd as explained above and Quaglia or DeAngelis. In the paper Dreassi teaches quantitative analysis of lamotrigine in plasma and tablets by planar chromatography and comparison with liquid chromatography and UV spectrophotometry. A method using planar chromatography (PC) was developed for determining lamotrigine (LTG) in human plasma and in tablets. LTG was extracted with MeCN in the presence of Na_2CO_3. 3,5-Diamino-6-(2-methoxyphenyl)- 1,2,4-triazine was used as internal standard. The detection limit was 0.27 μg/mL plasma and the recovery from human plasma fortified with various concentrations of LTG was 91.3%. No interference from other common antiepileptic agents was found. The results obtained with the PC method were compared with those obtained by a method using liquid chromatography for analysis of plasma and tablets. On page 1278 Dreassi teaches the formation of calibration standards and the operating conditions including the method of quantification. Dreassi does not teach the quantification of any impurities.

In the paper Quaglia teaches the determination of chlorthalidone and its impurities in bulk and in dosage forms by high-performance thin-layer chromatographic densitometry. Chlorthalidone and its impurities were determined in bulk and pharmaceuticals by high-performance TLC-densitometry with dioxane-iso-PrOH-25% NH_4OH-toluene-xylene (30:30:20:10:10) as the mobile phase. The relative standard deviation was 1.9% and the

recovery of chlorthalidone and the impurities from artificial mixtures was 96.4-102.0%. Pages 436-437 teach the preparation of standards for Chlorthalidone and two of its impurities which were then used for calibration and calculation of the actual concentration. See figure 1 for an example chromatogram. The method was simple, accurate, reproducible, and selective.

In the paper DeAngelis describes a quantitative thin-layer chromatography (TLC) procedure for the analysis of the anticonvulsant cinromide (I, 3-bromo-N-ethylcinnamamide) [58473-74-8] and its 2 major metabolites, 3-bromocinnamamide [71539-43-0] and 3-bromocinnamic acid [32862-97-8], in plasma of the dog. These compounds were recovered from acidified plasma by extraction into benzene, with a recovery of 95%. All 3 compounds were quantitated directly on a TLC plate by UV absorbance densitometry at 270 nm. The linear range for the quantification of the compounds on a TLC plate was 10-1000 ng. The complete procedure is useful in the range 50-100 g/mL plasma, with a relative standard deviation of about 10%. The specificity of the method for the parent drug and each of its metabolites was confirmed by high-performance liquid chromatography. The method was used to determine the pharmacokinetics of cinromide and its 2 major plasma metabolites in dogs following a single oral dose of the drug. Pages 354-356 teach the preparation of standards of each of the compounds and the spotting of these standards and samples on to the TLC plates for quantification and verification of the samples.

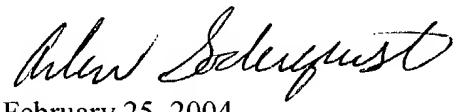
It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the planar and liquid chromatography methods of Dreassi to determine stability/impurities in the tablet or other formulations of lamotrigine as taught by Floyd using standards of lamotrigine and it known impurities as taught by Floyd because as taught by Quaglia or DeAngelis standard compositions of the expected or known components in the composition assist in verifying and quantifying the components of pharmaceutical formulations.

9. Applicant's arguments filed December 18, 2003 have been fully considered but they are not persuasive. Applicant should note that each of claims 12-15 are the rejected portion of original claims 1, 2, 4 and 11. The primary reason for not making this action final is that the WO publication of the Floyd patent is used in the rejections because it is anticipatory under 35 USC 102(b).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose current telephone number is (571) 272-1265 as a result of the examiner moving to the new USPTO location. The examiner's schedule is variable between the hours of about 5:30 AM to about 5:00 PM on Monday through Thursday and alternate Fridays.

A general phone number for the organization to which this application is assigned is (571) 272-1700. The fax phone number to file official papers for this application or proceeding is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



February 25, 2004
ARLEN SODERQUIST
PRIMARY EXAMINER